Mikart

1929 '99 OCT 26 A9:27

October 8, 1999

Dockets Management Branch
Food and Drug Administration
Room 1061
Department of Health and Human Services
5630 Fishers Lane
Rockville, MD 20857

Dear Sir/Madam:

Mikart, Incorporated, respectfully submits the enclosed Citizen's Petition, in quadruplicate, for your review and consideration. If you have any questions concerning this petition, please contact me at the number and/or address below.

Sincerely,

Cerie B. McDonald
President
Mikart, Incorporated

Enclosures

99P-4648

CP1

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

Mikart

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Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

CITIZEN'S PETITION

The undersigned, Mikart, Incorporated, submits this petition under 21 CFR 314.122 of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to determine whether Carbinoxamine Maleate 4 mg/5 cc Elixir (NDA 8-955) was withdrawn from sale for reasons of safety and effectiveness.

A. ACTION REQUESTED

The Petitioner requests that the Commissioner of Food and Drugs amend the List of Drug Products Suitable for Abbreviated New Drug Applications (1998), and Supplement Ten (1999), to include the drug Carbinoxamine Maleate Elixir (4 mg per 5 cc).

B. STATEMENT OF GROUNDS

The above drug product meets the criteria for ANDA approval under 505(j) (2) (A) & (c) of the Federal Food, Drug and Cosmetic Act as amended.

The drug product which is the subject of this Petition is deemed similar and related to the previously approved product Clistin Tablets, 4 mg, and Elixir, 4 mg/5 cc, originally manufactured by McNeil, now the property of R.W. Johnson. The proposed dosage form is a liquid. This dosage form is comparable with the dosage form listed in the reference drug. The drug dose is exactly 4 mg as listed in the reference drug. A copy of the reference listed drug labeling is included in Attachment A.

Proposed labeling for Carbinoxamine Maleate Liquid 4 mg per 5 mL is in Attachment B. A side by side comparison of labeling can be found in Attachment C.

A previous ruling in response to Docket No. 98-0062 CP1, a Citizen's Petition filed by Sage Pharmaceuticals, is found in Attachment D (63 Federal Register 98 pp. 27986-27987). This decision dealt with the issue that Carbinoxamine Maleate Tablets USP 4 mg were not withdrawn for reasons of safety and effectiveness. Given the similarity in the immediate release action of the tablets and the liquid, the Petitioner respectfully submits this information for review.

For the foregoing reasons, the undersigned requests the Commissioner to grant this Petition and to authorize submission and approval of an ANDA for a liquid form of Carbinoxamine Maleate (4 mg per 5 mL).

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

C. ENVIRONMENTAL IMPACT

The Petitioner claims an exemption under 25.24 (c)(1). The product which is the subject of the Petition is similar and related to drug products that are already being marketed, and there is no reason to conclude that marketing of such an additional drug will cause significant environmental effects.

D. ECONOMIC IMPACT

This information will be submitted on request of the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Cerie B. McDonald
President
Mikart, Incorporated
1750 Chattahoochee Avenue, N.W.
Atlanta, Georgia 30318
(404) 351-4510

ATTACHMENT A

LOG NO. 1883

CLISTIN

BEST AVAILABLE COPY

CLISTIN® (carbinoxamine maleate)	Tablets, 4 mg. Elixir, 4 mg./5 cc.	
CLISTIN® R-A (carbinoxamine maleate)	Repeat Action Tablets	 8 mg. 12 mg.
CLISTIN® Expectorant	Syrup, per 5 cc. CLISTIN (carbinoxamine maleate) 2 mg. Ammonium Chloride 120 mg. Sodium Citrate 120 mg. Potassium Guaiacolsulfonate 60 mg. Chloroform 0.01 cc. Benzyl Alcohol 0.3% (v/v)	
CLISTIN-D®	Tablets CLISTIN (carbinoxamine maleate) 2 mg. TYLENOL® (acetaminophen) 300 mg. Phenylephrine Hydrochloride 10 mg. Elixir, per 5 cc. CLISTIN (carbinoxamine maleate) 2 mg. TYLENOL (acetaminophen) 120 mg. Phenylephrine Hydrochloride 5 mg.	 

Tablets/Elixir/Tablets R-A *Antihistaminic*

CLISTIN® (carbinoxamine maleate)

Description CLISTIN (carbinoxamine maleate) is 2-[*p*-chloro-α-(2-dimethylaminoethoxy) benzyl] pyridine maleate, a potent and distinctive antihistaminic compound.

Single dose forms: Each scored, pink Tablet (imprinted "McNEIL") or each 5 cc. (1 teaspoonful) of the dark red Elixir (alcohol 7%) contains CLISTIN (carbinoxamine maleate) 4 mg.

Repeat dose forms: Tablets CLISTIN R-A (carbinoxamine maleate) (Repeat Action Tablets) 8 mg. (*orange* coated) and 12 mg. (*yellow* coated), imprinted "McNEIL."

Each Repeat Action Tablet contains CLISTIN (carbinoxamine maleate) in two equal doses, one in the outer coat for immediate release and one in the specially coated core for delayed action.

Caution: Federal law prohibits dispensing without prescription.

Action Antihistaminic. The clinical response to the tablets or elixir lasts 4 to 6 hours; the repeat action forms are effective for as long as 8 to 12 hours.

Indications CLISTIN (carbinoxamine maleate) is especially useful in the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis, urticaria, minor drug reactions, pruritic skin conditions, and as adjunctive therapy in asthma.

CLISTIN®

Advantages

1. *Unusually low incidence of side effects*—Clinical results indicate exceptional safety[1-4] and a very low incidence of drowsiness.
2. *Wide margin of safety* between therapeutic doses and toxic dose.[4]
3. *Exceptional palatability*—[illegible] (carbinoxamine maleate) is practically tasteless and will not produce [illegible] anesthesia of the mouth or throat. Both Tablets and the pleasantly flavored[5] Elixir assure patient acceptance.
4. *Convenience*—The varied dosage forms provide convenience in administration. The scored Tablets and Elixir give flexibility (particularly helpful with children), while the Repeat Action Tablets afford prolonged relief with doses [illegible] infrequently as every 8 to 12 hours.

Side Effects and Precautions Side effects are rare and are mild when they occur. As with any antihistaminic preparation, an occasional patient may note some drowsiness. If a sensitivity reaction occurs, the drug should be stopped.

Dosage and Administration CLISTIN (carbinoxamine maleate) is well tolerated in doses as high as 24 mg. daily, in divided doses, over prolonged periods. On the other hand, some patients may respond to as little as 4 mg. daily. Consequently, dosage should be based on the severity of the condition and the response of the patient.

Clinical experience indicates that the following dosage schedules are safe and effective:

	Adults	Children 1–3 yrs.	Children 3–6 yrs.	Over 6 yrs.
		given t.i.d. or q.i.d.		
Elixir	1 to 2 tsp. t.i.d. or q.i.d.	½ tsp.	½ to 1 tsp.	1 tsp.
Tablets	1 to 2 tabs. t.i.d. or q.i.d.	½ tab.	½ to 1 tab.	1 tab.
Tablets R-A, 8 mg.	1 tab. q. 8–12 h.	——	——	——
Tablets R-A, 12 mg.	1 tab. q. 12 h.	——	——	——

Indications. CLISTIN EXPECTORANT is useful for the treatment of cough associated with the common cold and other respiratory infections, such as bronchitis and tracheitis, and for the relief of symptoms associated with allergic disorders.

Advantages

1. *A preferred antihistamine*—*Clistin* (carbinoxamine maleate) "has as potent an antihistamine action and as low an incidence of side effects as has any other previously employed histamine antagonist."[1-3] Clinical use has confirmed its high order of effectiveness and safety in common allergies.[1-4]

2. *Time-tested expectorant action*—A combination of drugs which facilitates expectoration, accelerates resorption of inflammatory exudate, and exerts an additive antitussive effect, while minimizing the digestive disturbances usually associated with large individual doses of these drugs.[5]

3. *Non-narcotic*—CLISTIN EXPECTORANT does not contain a narcotic. Codeine phosphate, codeine sulfate or dihydrocodeinone bitartrate can be added in appropriate dosage if the physician so desires.

4. *Exceptional palatability*—The pleasant fruit flavor assures patient acceptance and ease of administration. The demulcent base soothes local irritation.

CLISTIN® EXPECTORANT

Syrup — *Antitussive Expectorant*

CLISTIN® EXPECTORANT

Description. Each 5 cc. (one teaspoonful) of yellow, fruit-flavored Syrup CLISTIN EXPECTORANT contains:

CLISTIN (carbinoxamine maleate)	2 mg.
Ammonium Chloride	120 mg. (2 gr.)
Sodium Citrate	120 mg. (2 gr.)
Potassium Guaiacolsulfonate	60 mg. (1 gr.)
Chloroform	0.01 cc. (1/6 min.)
Benzyl Alcohol	0.3% (v/v)

Caution: Federal law prohibits dispensing without prescription.

Action. CLISTIN EXPECTORANT is an effective antitussive and expectorant through the actions of *Clistin* (carbinoxamine maleate) an antihistamine which diminishes nasal congestion;[2] ammonium chloride and sodium citrate, demulcent expectorants which soothe inflammation by aiding the secretion of mucus, thus relieving dry, unproductive cough;[1,5] potassium guaiacolsulfonate, which stimulates the repair of inflamed mucosal lining;[5] chloroform, a demulcent expectorant and local analgesic;[5] and benzyl alcohol, which acts as an anesthetic on the irritated mucous membrane.[5]

Side Effects and Precautions. See CLISTIN (carbinoxamine maleate).

Dosage and Administration

Adults: One teaspoonful (5 cc.) every three hours or as directed by the physician.
Children (six years or older): One-half to one teaspoonful every three hours.

Tablets/Elixir

Decongestant-Analgesic

CLISTIN-D®

Description Each scored, light yellow Tablet CLISTIN-D (imprinted "McNEIL") contains:

CLISTIN® (carbinoxamine maleate)	2 mg.
TYLENOL® (acetaminophen)	300 mg.
Phenylephrine Hydrochloride	10 mg.

Each 5 cc. (one teaspoonful) amber-colored, orange-flavored Elixir CLISTIN-D (alcohol 7%) contains:

CLISTIN (carbinoxamine maleate)	2 mg.
TYLENOL (acetaminophen)	120 mg.
Phenylephrine Hydrochloride	5 mg.

Caution: Federal law prohibits dispensing without prescription.

Action CLISTIN-D affords relief of symptoms of the common cold and allergic disorders through the actions of *Clistin* (carbinoxamine maleate) a potent antihistamine which diminishes nasal congestion,[2] *Tylenol* (acetaminophen) a non-salicylate analgesic-antipyretic which is unlikely to irritate the gastrointestinal tract,[11-13] and phenylephrine hydrochloride, a vasoconstricting decongestant which is effective on oral administration.[14]

Indications CLISTIN-D Tablets and Elixir are indicated for the relief of nasal congestion and other discomforts associated with common colds, sinusitis, and allergic or vasomotor rhinitis.

Advantages

1. *A preferred antihistamine—Clistin* (carbinoxamine maleate) "has as potent an antihistamine action and as low an incidence of side effects as has any other previously employed histamine antagonist."[3] Clinical use has confirmed a high order of effectiveness and safety.[1-4]
2. *An exceptionally safe, nonsalicylate analgesic-antipyretic—Tylenol* (acetaminophen) relieves fever and pain with little likelihood of gastric irritation or ulcer exacerbation[11-13]—a preferred analgesic in the treatment of skeletal muscle pain.[14]
3. *Phenylephrine hydrochloride* effectively relieves nasal congestion on oral administration.[14]

Side Effects and Precautions See CLISTIN (carbinoxamine maleate).

Dosage and Administration

Tablets CLISTIN-D. *Adults*, 2 tablets three or four times daily.

Elixir CLISTIN-D. *Children* (1 to 6 years), ½ to 1 teaspoonful every 4 hours. *Children* (6 years and older), 1 to 2 teaspoonfuls every 4 hours. *Adults*, 2 teaspoonfuls every 4 hours.

CLISTIN-D®

(carbinoxamine maleate)

References

1. Johnson, H. L., Jr.: Amer. Practit. 5:862-863 (Nov.) 1954.
2. Grant, B. R., et al.: J. Allergy 27:37-42 (Jan.) 1956.
3. Beale, H. D., et al.: J. Allergy 26:531-534 (Nov.) 1954.
4. MacLaren, W. R., et al.: Ann. Allergy 13:307-312 (May-June) 1955.
5. A.M.A. Council on Drugs: New and Nonofficial Drugs 1964, Philadelphia, J. B. Lippincott Company, 1964, p. 23.
6. Marsh, D. F.: J. Pharmacol. Exp. Ther. 110:35 (Jan.) 1954.
7. Halpern, B. A.: Antiemetic Agents, in Modell, W.: Drugs of Choice 1963-1964, St. Louis, C. V. Mosby Company, 1964, (a) pp. 369-370; (b) p. 385; (c) p. 384.
8. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1955, pp. 1069-1071.
9. Eellman, T.: A Manual of Pharmacology, ed. 8, Philadelphia, W. B. Saunders Company, 1957, (a) p. 340; (b) p. 583.
10. Bengel, A. L.: JAMA 148:501-504 (Feb. 14) 1952.
11. Roth, J. L., A.: Med. Clin. N. Amer. 41:1517-1530 (Nov.) 1957.
12. Roth, J. L. A., et al.: Postgrad. Med. 28:443-449 (Nov.) 1960.
13. Roth, J. L. A., et al.: Gastroenterology 44:648-658 (Feb.) 1963.
14. Hutcheson, R. C., and Ostrander, A. J.: Fed. Proc. 14:306-307 (Mar.) 1955.

ATTACHMENT B

Carbinoxamine Maleate Liquid 4 mg per 5 mL

Rx Only

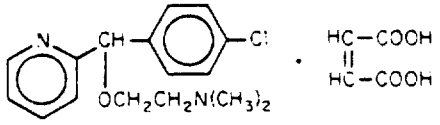
Code 000000
Rev. 10/99

DESCRIPTION:

Each 5 mL (1 Teaspoon) of liquid contains:

Carbinoxamine Maleate ..... 4 mg

Carbinoxamine Maleate (2-[p-Chloro-α-[2-(dimethylamino)ethoxy]benzyl]pyridine maleate) is a potent and distinctive antihistaminic compound. It has the following structural formula:



MW = 406.87

CLINICAL PHARMACOLOGY

Carbinoxamine maleate possesses H_1 antihistaminic activity and mild anticholinergic and sedative effects. Serum half-life for Carbinoxamine is estimated to be 10 to 20 hours. Virtually no intact drug is excreted in the urine.

CONTRAINDICATIONS

Patients with hypersensitivity or idiosyncrasy to any ingredients, patients taking MAO (monoamine oxidase) inhibitors, patients with narrow-angle glaucoma, urinary retention, severe hypertension, peptic ulcer, or coronary artery disease, or patients undergoing an asthmatic attack.

ACTION

Antihistaminic.

INDICATIONS AND USAGE

Carbinoxamine Maleate is especially useful in the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis, urticaria, minor drug reactions, and pruritic skin conditions.

PRECAUTIONS

General

Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, increased intraocular pressure, diabetes mellitus, and prostatic hypertrophy.

Information for Patients

Avoid alcohol, and other CNS depressants while taking this product. Patients sensitive to antihistamines may experience moderate to severe drowsiness.

WARNINGS

Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, prostatic hypertrophy, increased intraocular pressure, diabetes mellitus and prostatic hypertrophy.

Drug Interactions

Antihistamines may enhance the effects of tricyclic antidepressants, barbiturates, alcohol, and other CNS depressants. MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No data are available on the long-term potential of the components of the product for carcinogenesis, mutagenesis, or impairment of fertility in animals or humans.

Pregnancy

Category C

Animal reproduction studies have not been conducted with this product. It is also not known whether this product can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Give to pregnant women only if clearly needed.

Nursing Mothers

Small amounts of antihistamines are excreted in breast milk. Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, this product is contraindicated in nursing mothers. Also, antihistamines may inhibit lactation because of their anticholinergic effects.

Pediatric Use

The use of this drug is not recommended in newborn or premature infants because this age group has an increased susceptibility to anticholinergic side effects such as central nervous system (CNS) excitation, and an increased tendency toward convulsions. In infants and children, antihistamines in overdosage may cause hallucinations, convulsions, or death. This product is not recommended for children under 6 years of age. As in adults, antihistamines may diminish mental alertness in children. In young children in particular, they may produce excitation. In older children taking antihistamines, a paradoxical reaction characterized by hyperexcitability may occur.

Geriatric Use

Confusion, dizziness, sedation, hypotension, hyperexcitability, and anticholinergic side effects, such as dryness of month and urinary retention (especially in males), maybe more likely to occur in geriatric patients taking antihistamines.

ADVERSE REACTIONS

Antihistamines: Sedation, dizziness, diplopia, vomiting, diarrhea, dry mouth, headache, nervousness, nausea, anorexia, heartburn, weakness, polyuria and dysuria and rarely, excitability in children.

Side effects are rare and are mild when they occur. As with any antihistaminic preparation, an occasional patient may note some drowsiness. If a sensitivity reaction occurs, use of the drug should be discontinued.

OVERDOSAGE

Should antihistamine effects predominate, central action constitutes the greatest danger. In small children, symptoms include excitation, hallucination, ataxia, incoordination tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma, and death may occur in severe cases. In adults fever and flushing are uncommon; excitement leading to convulsions and physical depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed, blood

pressure is usually stable. Should sympathomimetic symptoms predominate, central effects include restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability and insomnia. Cardiovascular and renal effects include difficulty in micturition, headache, flushing palpitation, cardiac arrhythmias, hypertension with subsequent, hypotension and circulatory collapse. Gastrointestinal effects include dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea and abdominal cramps.

Treatment

Evacuate stomach as condition warrants. Activated charcoal may be useful. Maintain a nonstimulating environment. Monitor cardiovascular status. Do not give stimulants. Reduce fever with cool sponging. Support respiration. Use sedatives or anticonvulsants to control CNS excitation and convulsions. Physostigmine may reverse anticholinergic symptoms.

DOSAGE AND ADMINISTRATION

	Children		
Adults	1-3 yrs.	3-4 yrs.	Over 6 yrs.
1 to 2 tsp. (5 -10 mL)	Given t.i.d. or q.i.d.		
t.i.d or q.i.d.	1/2 tsp. (2.5 mL)	1/2 to 1 tsp. (2.5 - 5 mL)	1 tsp. (5 mL)

t.i.d. = three times a day
q.i.d. = four times a day
mL = milliliter
tsp. = teaspoon

Carbinoxamine maleate is well tolerated in doses as high as 24 mg daily, in divided doses, over prolonged periods. On the other hand, some patients respond to as little as 4 mg. Consequently, dosage should be based on the severity of the condition and the responses of the patient.

HOW SUPPLIED

Carbinoxamine Maleate Liquid (4 mg per 5 mL) containing Carbinoxamine Maleate 4 mg per 5 mL is a clear, colorless liquid supplied in 1 oz. bottles, 4 oz. bottles, and 16 oz. bottles.

Storage: Store at controlled room temperature 15°- 30°(59°-86°F).

KEEP THIS DRUG AND ALL DRUGS OUT OF THE REACH OF CHILDREN

Dispensing: Dispense in tight, light-resistant container with a child-resistant closure.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 10/99 Code 000000

ATTACHMENT C

SIDE BY SIDE INSERT LABELING COMPARISON OF THE REFERENCE DRUG CLISTIN, AND CARBINOXAMINE MALEATE LIQUID 4 MG PER 5 ML

1. The reference listed drug states "Tablets/Elixir/Tablets R-A Clistin (Carbinoxamine Maleate)". Mikart's proposed drug states "Carbinoxamine Maleate Liquid 4 mg per 5 mL".

2. The reference listed drug states "Single dose forms: each 5 cc (1 teaspoonful) of the dark red Elixir (Alcohol 7 %) contains Clistin (Carbinoxamine Maleate) 4 mg". Mikart's proposed drug states "Each 5 mL (1 teaspoon) of liquid contains (Carbinoxamine Maleate) 4 mg".

3. The reference listed drug has "Caution: Federal Law prohibits dispensing without Prescription". Mikart's proposed drug states "Rx only".

4. Clinical Section

   The reference listed drug states "Usually low Incidence of side effects-Clinical results indicate exceptional safety and a very low incidence of drowsiness". Mikart's proposed drug states "Carbinoxamine maleate possesses H_1 antihistaminic activity and mild anticholinergic and sedative effects. Serum half-life for Carbinoxamine is estimated to be 10 to 20 hours. Virtually no intact drug is excreted in the urine".

5. The reference listed drug does not contain any of the following sections:

   - General Precautions

   - Information for Patients

   - Warnings

   - Drug Interactions

   - Carcinogenesis, Mutagenesis, Impairment of Fertility

   - Pregnancy

   - Nursing Mothers

   - Pediatric Use

   - Geriatric Use

   - Overdosage & Treatment

   - KEEP THIS DRUG AND ALL DRUGS OUT OF THE REACH OF CHILDREN

   - Storage

   - Dispensing

6. The reference listed drug has pictures of dosage forms. Mikart's proposed drug product does not have any pictures of dosage forms.

7. The proposed drug does have a " Manufactured by " statement. The reference listed drug does not have a "Manufactured by" statement.

8. The proposed drug has a code and a revision date. The reference listed drug does not have a code or a revision date.

9. The reference listed drug has "Antihistaminic" at the beginning of the insert. The proposed insert does not have "Antihistaminic" at the beginning of the insert.

10. The reference listed drug does not have a structure for Carbinoxamine Maleate. The proposed insert has a structure for Carbinoxamine Maleate.

SIDE BY SIDE COMPARISON BETWEEN CLISTIN AND CARBINOXAMINE MALEATE 4 MG PER 5 ML

Tablets/Elixir/Tablets R-A (1) (9) *Antihistaminic*

CLISTIN® (carbinoxamine maleate)

Description CLISTIN (carbinoxamine maleate) is 2-[p-chloro-α-(2-dimethylaminoethoxy) benzyl] pyridine maleate, a potent and distinctive antihistaminic compound.

(2)

Single dose forms: Each scored, pink Tablet (imprinted "McNEIL") or each 5 cc. (1 teaspoonful) of the dark red Elixir (alcohol 7%) contains CLISTIN (carbinoxamine maleate) 4 mg.

Repeat dose forms: Tablets CLISTIN R-A (carbinoxamine maleate) (Repeat Action Tablets) 8 mg. (*orange coated*) and 12 mg. (*yellow coated*), imprinted "McNEIL."

Each Repeat Action Tablet contains CLISTIN (carbinoxamine maleate) in two equal doses, one in the outer coat for immediate release and one in the specially coated core for delayed action.

(5) *Caution:* Federal law prohibits dispensing without prescription.

Action Antihistaminic. The clinical response to the tablets or elixir lasts 4 to 6 hours; the repeat action forms are effective for as long as 8 to 12 hours.

Indications CLISTIN (carbinoxamine maleate) is especially useful in the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis, urticaria, minor drug reactions, pruritic skin conditions, and as adjunctive therapy in asthma.

(1) Carbinoxamine Maleate Liquid 4 mg per 5 mL

Rx Only

(8)

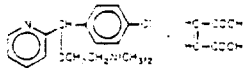
Code 000000
Rev. 10/99

(2) **DESCRIPTION:**
Each 5 mL (1 Teaspoon) of liquid contains:

Carbinoxamine Maleate	4 mg

Carbinoxamine Maleate (2-[p-Chloro-α-[2-(dimethylamino)ethoxy]benzyl]pyridine maleate) is a potent and distinctive antihistaminic compound. It has the following structural formula:

(10)



MW = 406.87

(4)

CLINICAL PHARMACOLOGY
Carbinoxamine maleate possesses H_1 antihistaminic activity and mild anticholinergic and sedative effects. Serum half-life for Carbinoxamine is estimated to be 10 to 20 hours. Virtually no intact drug is excreted in the urine.

CONTRAINDICATIONS
Patients with hypersensitivity or idiosyncrasy to any ingredients, patients taking MAO (monoamine oxidase) inhibitors, patients with narrow-angle glaucoma, urinary retention, severe hypertension, peptic ulcer, or coronary artery disease, or patients undergoing an asthmatic attack.

ACTION
Antihistaminic.

INDICATIONS AND USAGE
Carbinoxamine Maleate is especially useful in the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis, urticaria, minor drug reactions, and pruritic skin conditions.

(5) **PRECAUTIONS**
General
Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, increased intraocular pressure, diabetes mellitus, and prostatic hypertrophy.

(5) **Information for Patients**
Avoid alcohol, and other CNS depressants while taking this product. Patients sensitive to antihistamines may experience moderate to severe drowsiness.

SIDE BY SIDE COMPARISON BETWEEN CLISTIN AND CARBINOXAMINE MALEATE 4 MG PER 5 ML

CLISTIN® (carbinoxamine maleate)	Tablets, 4 mg. Elixir, 4 mg./5 cc.		
CLISTIN® R-A (carbinoxamine maleate)	Repeat Action Tablets	8 mg.	12 mg.
CLISTIN® Expectorant	Syrup, per 5 cc. CLISTIN (carbinoxamine maleate) Ammonium Chloride Sodium Citrate Potassium Guaiacolsulfonate Chloroform Benzyl Alcohol	2 mg. 120 mg. 120 mg. 60 mg. 0.01 cc. 0.3% (v/v)	
CLISTIN-D®	Tablets CLISTIN (carbinoxamine maleate) TYLENOL® (acetaminophen) Phenylephrine Hydrochloride	2 mg. 300 mg. 10 mg.	
	Elixir, per 5 cc. CLISTIN (carbinoxamine maleate) TYLENOL (acetaminophen) Phenylephrine Hydrochloride	2 mg. 120 mg. 5 mg.	

SIDE BY SIDE COMPARISON BETWEEN CLISTIN AND CARBINOXAMINE MALEATE 4 MG PER 5 ML

(4)

Advantages

1. ***Unusually low incidence of side effects***—Clinical results indicate exceptional safety[1-3] and a very low incidence of drowsiness.
2. ***Wide margin of safety*** between therapeutic dose and toxic dose.[4]
3. ***Exceptional palatability***—[illegible] (carbinoxamine maleate) is practically tasteless and will not produce [illegible] anesthesia of the mouth or throat. Both Tablets and the pleasantly flavored Elixir assure patient acceptance.
4. ***Convenience***—The varied dosage forms provide convenience in administration. The scored Tablets and Elixir give flexibility (particularly helpful with children), while the Repeat Action Tablets afford prolonged relief with doses [illegible] as infrequently as every 8 to 12 hours.

Side Effects and Precautions Side effects are rare and are mild when they occur. As with any antihistaminic preparation, an occasional patient may note some drowsiness. If a sensitivity reaction occurs, the drug should be stopped.

(5) **WARNINGS**

Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, prostatic hypertrophy, increased intraocular pressure, diabetes mellitus and prostatic hypertrophy.

(5) **Drug Interactions**

Antihistamines may enhance the effects of tricyclic antidepressants, barbiturates, alcohol, and other CNS depressants. MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.

(5) **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No data are available on the long-term potential of the components of the product for carcinogenesis, mutagenesis, or impairment of fertility in animals or humans.

(5) **Pregnancy**

Category C

Animal reproduction studies have not been conducted with this product. It is also not known whether this product can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Give to pregnant women only if clearly needed.

(5) **Nursing Mothers**

Small amounts of antihistamines are excreted in breast milk. Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, this product is contraindicated in nursing mothers. Also, antihistamines may inhibit lactation because of their anticholinergic effects.

(5) **Pediatric Use**

The use of this drug is not recommended in newborn or premature infants because this age group has an increased susceptibility to anticholinergic side effects such as central nervous system (CNS) excitation, and an increased tendency toward convulsions. In infants and children, antihistamines in overdosage may cause hallucinations, convulsions, or death. This product is not recommended for children under 6 years of age. As in adults, antihistamines may diminish mental alertness in children. In young children in particular, they may produce excitation. In older children taking antihistamines, a paradoxical reaction characterized by hyperexcitability may occur.

(5) **Geriatric Use**

Confusion, dizziness, sedation, hypotension, hyperexcitability, and anticholinergic side effects, such as dryness of month and urinary retention (especially in males), maybe more likely to occur in geriatric patients taking antihistamines.

ADVERSE REACTIONS

Antihistamines: Sedation, dizziness, diplopia, vomiting, diarrhea, dry mouth, headache, nervousness, nausea, anorexia, heartburn, weakness, polyuria and dysuria and rarely, excitability in children.

Side effects are rare and are mild when they occur. As with any antihistaminic preparation, an occasional patient may note some drowsiness. If a sensitivity reaction occurs, use of the drug should be discontinued.

(5) **OVERDOSAGE**

Should antihistamine effects predominate, central action constitutes the greatest danger. In small children, symptoms include excitation, hallucination, ataxia, incoordination tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma, and death may occur in severe cases. In adults fever and flushing are uncommon; excitement leading to convulsions and physical depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed, blood

SIDE BY SIDE COMPARISON BETWEEN CLISTIN AND CARBINOXAMINE MALEATE 4 MG PER 5 ML

Dosage and Administration Clistin (carbinoxamine maleate) is well tolerated in doses as high as 24 mg. daily, in divided doses, over prolonged periods. On the other hand, some patients respond to as little as 4 mg. daily. Consequently, dosage should be based on the severity of the condition and the response of the patient.

Clinical experience indicates that the following dosage schedules are safe and effective:

	Adults	Children 1-3 yrs.	Children 3-6 yrs.	Over 6 yrs.
		given t.i.d. or q.i.d.		
Elixir	1 to 2 tsp. t.i.d. or q.i.d.	½ tsp.	½ to 1 tsp.	1 tsp.
Tablets	1 to 2 tabs. t.i.d. or q.i.d.	½ tab.	½ to 1 tab.	1 tab.
Tablets R-A, 8 mg.	1 tab. q. 8-12 h.	———	———	———
Tablets R-A, 12 mg.	1 tab. q. 12 h.	———	———	———

pressure is usually stable. Should sympathomimetic symptoms predominate, central effects include restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability and insomnia. Cardiovascular and renal effects include difficulty in micturition, headache, flushing palpitation, cardiac arrhythmias, hypertension with subsequent, hypotension and circulatory collapse. Gastrointestinal effects include dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea and abdominal cramps.

(5) **Treatment**
Evacuate stomach as condition warrants. Activated charcoal may be useful. Maintain a nonstimulating environment. Monitor cardiovascular status. Do not give stimulants. Reduce fever with cool sponging. Support respiration. Use sedatives or anticonvulsants to control CNS excitation and convulsions. Physostigmine may reverse anticholinergic symptoms.

DOSAGE AND ADMINISTRATION

Adults	Children 1-3 yrs.	Children 3-4 yrs.	Children Over 6 yrs.
1 to 2 tsp. (5 -10 mL) t.i.d or q.i.d.	Given t.i.d. or q.i.d.		
	1/2 tsp. (2.5 mL)	1/2 to 1 tsp. (2.5 - 5 mL)	1 tsp. (5 mL)

t.i.d. = three times a day
q.i.d. = four times a day
mL = milliliter
tsp. = teaspoon

Carbinoxamine maleate is well tolerated in doses as high as 24 mg daily, in divided doses, over prolonged periods. On the other hand, some patients respond to as little as 4 mg. Consequently, dosage should be based on the severity of the condition and the responses of the patient.

HOW SUPPLIED

Carbinoxamine Maleate Liquid (4 mg per 5 mL) containing Carbinoxamine Maleate 4 mg per 5 mL is a clear, colorless liquid supplied in 1 oz. bottles, 4 oz. bottles, and 16 oz. bottles.

(5) **Storage:** Store at controlled room temperature 15°-30°(59°-86°F).

(5) **KEEP THIS DRUG AND ALL DRUGS OUT OF THE REACH OF CHILDREN**

(5) **Dispensing:** Dispense in tight, light-resistant container with a child-resistant closure.

(7)
Manufactured by:
MIKART, INC.
Atlanta, GA 30318

(8) Rev. 10/99

(8) Code 000000

ATTACHMENT D

withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved (Sec. 314.161(a)(1) (21 CFR 314.161(a)(1))). FDA may not approve an ANDA that does not refer to a listed drug.

In a citizen petition dated January 22, 1998 (Docket No. 98P-0062/CP1), submitted in accordance with 21 CFR 314.122, Sage Pharmaceuticals requested that the agency determine whether carbinoxamine maleate (Clistin<Register>) 4-mg immediate-release tablets were withdrawn from sale for reasons of safety or effectiveness. Carbinoxamine maleate (Clistin<Register>) 4-mg immediate-release tablets were the subject of approved NDA 8-915.\1\ On

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January 26, 1993, the R. W. Johnson Pharmaceutical Research Institute notified FDA in writing that carbinoxamine maleate (Clistin<Register>) 4-mg immediate-release tablets were no longer being marketed under NDA 8-915 and requested the withdrawal of that application. FDA complied and announced the withdrawal of approval for NDA 8-915 in the Federal Register of March 2, 1994 (59 FR 9989).

\1\ NDA 8-915 also covered Clistin<Register> R-A, a controlled-release form of carbinoxamine maleate tablets. In the Federal Register of July 29, 1983 (48 FR 34514), FDA withdrew approval of NDA 8-915 as it pertained to Clistine<Register> R-A because no person submitted bioavailability data showing that the product was effective as a controlled-release dosage form.

FDA has reviewed its records and, under Sec. 314.161, has determined that carbinoxamine maleate 4-mg immediate-release tablets were not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will maintain carbinoxamine maleate 4-mg immediate-release tablets in the ``Discontinued Drug Product List'' section of the Orange Book. The ``Discontinued Drug Product List'' identifies, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDA's that refer to carbinoxamine maleate 4-mg immediate-release tablets may be approved by the agency.

Dated: May 13, 1998.
William K. Hubbard,
Associate Commissioner for Policy Coordination.
[FR Doc. **98-13468 Filed** 5-20-**98**; 8:45 am]
BILLING CODE 4160-01-F

[Federal Register: May 21, 1998 (Volume 63, Number 98)]
[Notices]
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From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr21my98-117]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. 98P-0062]

Determination That Carbinoxamine Maleate 4-Milligram Immediate-Release Tablets Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that carbinoxamine maleate (Clistin<Register>) 4-milligram (mg) immediate-release tablets were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDA's) for carbinoxamine maleate 4-mg immediate-release tablets.

FOR FURTHER INFORMATION CONTACT: Richard L. Schwartzbard, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20855, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the ``listed drug,'' which is a version of the drug that was previously approved under a new drug application (NDA). Sponsors of ANDA's do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments included what is now section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(6)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the ``Approved Drug Products with Therapeutic Equivalence Evaluations,'' which is generally known as the ``Orange Book.'' Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162). Regulations also provide that the agency must make a determination as to whether a listed drug was

Fold at line over top of envelope to the right of the return address

CERTIFIED

Return Receipt
Z 357 966 651
Requested

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DOCKETS MANAGEMENT BRANCH
FOOD AND DRUG ADMINISTRATION
ROOM 1061
DEPARTMENT OF HEALTH AND HUMAN SERVICES
5630 FISHERS LANE
ROCKVILLE, MD 20857